Effects of Smoked Marijuana of Varying Potency on Ventilatory Drive and Metabolic Rate[1,2]

HUEY-DONG WU,[3] ROBERT S. WRIGHT, CATHERINE S. H. SASSOON, and DONALD P. TASHKIN

SUMMARY Ventilatory responses to hypercapnia in experienced marijuana smokers have previously been shown to decrease, increase, or not change acutely after marijuana. In one study, minute ventilation ($\dot{V}E$) and O_2 consumption ($\dot{V}O_2$) increased but hypoxic ventilatory response did not change after smoking marijuana. We further investigated the effects of marijuana of increasing potency (0, 13, and 20 mg THC) on ventilatory and mouth occlusion pressure ($P_{0.1}$) responses to hypercapnia and hypoxia in 11 young, healthy men who smoked marijuana regularly but refrained from any smoked substance, alcohol, caffeine, or other drugs for ≥ 12 h before study. Ventilatory and $P_{0.1}$ responses to hypoxia and hypercapnia were measured on 3 separate days before and 5 and 35 min (hypoxia) and 15 and 45 min (hypercapnia) after smoking. In a companion 3-day study, 12 young male habitual marijuana smokers underwent measurements of $\dot{V}E$, $\dot{V}O_2$, and CO_2 production ($\dot{V}CO_2$) before and 5 to 135 min after smoking marijuana containing 0, 15, or 27 mg THC. None of the active marijuana preparations caused significant changes in ventilatory or $P_{0.1}$ responses to either hypercapnia or hypoxia or in resting $\dot{V}E$, $\dot{V}O_2$ or $\dot{V}CO_2$. We conclude that smoking marijuana (13 to 27 mg THC) has no acute effect on central or peripheral ventilatory drive or metabolic rate in habitual marijuana smokers. These conclusions cannot be applied to infrequent users of marijuana without further study.

AM REV RESPIR DIS 1992; 146:716-721

Introduction

Marijuana remains the most commonly used illicit substance in the United States, with an estimated lifetime prevalence among high school seniors in 1990 of 40.7% (1). Because Δ^9-tetrahydrocannabinol (THC) has potent psychophysiologic properties, its effects on central ventilatory control have been investigated (2–4). Ventilatory responses to hypercapnia in previous users of marijuana have been shown by different investigators to decrease (3), increase (4), or not change (2) acutely following marijuana. In the only published study, no change in the ventilatory response to eucapnic hypoxia was observed after smoking 11 mg THC (4), but the same dose of THC appeared to stimulate both ventilation and metabolism.

The present study was carried out to investigate the effects of escalating doses of THC administered in smoked marijuana on the ventilatory and mouth occlusion pressure ($P_{0.1}$) responses to both hypercapnia and hypoxia and on resting minute ventilation and metabolic rate in young, healthy experienced male users of marijuana.

Methods

Phase 1

A group of 11 healthy white men (age 34.2 ± 7.6 yr, range 21 to 46 yr) who reported habitual smoking of marijuana (> 10 marijuana "joints" or the equivalent per week for ≥ 5 yr) were recruited from an ongoing study of the chronic pulmonary effects of frequent, regular marijuana use (5). No subject had a history of intravenous drug abuse, chronic cardiopulmonary disease, or recent respiratory tract infection. Each signed an informed consent form approved by the Human Subject Protection Committee of the University of California at Los Angeles (UCLA) School of Medicine. Initially, all subjects underwent a detailed respiratory and drug use questionnaire and a battery of pulmonary function tests, as previously described (5). Measured values for spirometry and diffusing capacity were compared with expected values using standard prediction equations (6, 7). The control of breathing studies were conducted at the same time of day on 3 separate days separated by 1 to 2 wk. Subjects were asked to refrain from using antihistamines for ≥ 72 h, sedative or stimulant drugs for ≥ 24 h, cannabis, coffee, tea, and alcohol for ≥ 12 h, and tobacco for ≥ 2 h before each study.

On each study day, an intravenous catheter was inserted for serial sampling of blood before and after marijuana smoking for subsequent measurement of serum THC concentration by radioimmunoassay (RIA) (8). Following catheter insertion, baseline measurements were performed in duplicate, including heart rate, functional residual capacity (FRC), and airway resistance (Raw) using a constant-volume body plethysmograph (9, 10), and ventilatory and mouth occlusion pressure responses to hypoxia and hypercapnia (see subsequent discussion). In random order, using a double-blind, crossover design, subjects then smoked a marijuana cigarette supplied by the National Institute on Drug Abuse (NIDA) weighing 832, 764, or 833 mg with a THC concentration of 0 (placebo), 1.55% (13 mg), or 2.65% (20 mg), respectively. Each subject smoked the marijuana cigarette according to his own customary technique, which we previously characterized (11). A forceps was used to hold the cigarette butt to facilitate complete consumption of the marijuana cigarette, including the butt, where THC is concentrated (12). After completion of smoking, venous blood was sampled, subjects subjectively rated their level of intoxication ("high") on a scale of 0 to 100 (100 being the greatest high they had ever experienced), and measurements of heart rate, body plethysmography, and ventilatory and mouth occlusion pressure responses to hypoxia and hypercapnia were repeated according to the following schedule. Venous blood was sampled at 0 to 2, 15, 30, and 45 min after smoking. Heart rate was measured at the same time intervals. Plethysmographic measurements were performed at 2 to 4 and 30 min. Hypoxic control of breathing responses was measured at 5 and 35 min and hypercapnic responses at 15 and 45 min after smoking.

Hypoxic responses were determined using the technique of Rebuck and Campbell (13). Arterial oxygen saturation (Sa_{O_2}) was measured continuously with an ear oximeter (Model IIA; Biox, Boulder, CO). In the seated position with nose clips applied, subjects

(Received in original form December 13, 1991 and in revised form April 15, 1992)

[1] From the Department of Clinical Pathology and Medicine, National Taiwan University Hospital, Taipei, the Departments of Medicine, University of California at Los Angeles and University of California at Irvine, and the Veterans Affairs Medical Center, Long Beach, California.

[2] Correspondence and requests for reprints should be addressed to Donald P. Tashkin, M.D., Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024.

[3] Supported by Grant No. RO1 DA 03018 from the National Institute on Drug Abuse.

breathed room air through a rubber mouthpiece via a three-way valve while expired gas was continuously sampled at the mouthpiece and analyzed for CO_2 concentration using a rapidly responding infrared CO_2 analyzer (Model PM-20; Cavitron, Paramus, NJ). After a stable end-tidal CO_2 concentration was achieved, subjects rebreathed the gas from a 13-L rolling-seal electronic spirometer (Model 220; Cardio-Pulmonary Instruments, Inc.) primed with their own expired air. During rebreathing, end-expired CO_2 was maintained constant at or close to the baseline level by pumping the spirometer gas through a canister containing soda lime CO_2 absorbent at a variable speed using a rheostat-controlled pump. Mouth pressure was recorded with a differential pressure transducer (Model MP45, sensitivity ±29 cm H_2O; Validyne Corp., Northridge, CA). Approximately every 15 s without the subject's knowledge, the inspiratory line was occluded for less than 0.5 s with a pneumatic inflatable balloon (Series 9327; Hans-Rudolph, Kansas City, MO). Tidal volume (V_T), minute ventilation ($\dot{V}_E$), mouth pressure, arterial O_2 saturation, and expired CO_2 concentration were continuously recorded on a multichannel oscilloscopic recorder with photographic attachment (Model VR-12; Honeywell, Pleasantville, NY). Mouth pressure 0.1 s after each inspiratory occlusion was measured manually from each tracing. $\dot{V}_E$ and $P_{0.1}$ were plotted against Sa_{O_2} on linear coordinates and the slopes were calculated by least-squares linear regression.

Ventilatory and $P_{0.1}$ responses to hypercapnia were measured using the Read rebreathing technique (14). In the seated position with nose clips in place, subjects again breathed room air through a three-way valve until the end-tidal CO_2 concentration sampled at the mouthpiece was stable. The valve was then turned so that subjects rebreathed a gas mixture from the spirometer consisting of 7% CO_2 and 93% O_2 in a volume equal to each subject's FVC plus 1 L. Once a satisfactory rebreathing plateau was achieved, rebreathing continued until the P_{CO_2} rose 15 mm Hg above the rebreathing plateau (usually less than 4 to 5 min). V_T, $\dot{V}_E$, $P_{0.1}$, and P_{CO_2} were measured and recorded as indicated previously. $\dot{V}_E$ and $P_{0.1}$ were plotted against the P_{CO_2}, and the slopes of the ventilatory and $P_{0.1}$ responses to hypercapnia were calculated by least-squares linear regression using the equation $\dot{V}_E$ or $P_{0.1} = S(P_{CO_2} - B)$, where S is the slope and B is the extrapolated intercept on the abscissa (P_{CO_2} axis). From the same plot, $\dot{V}_E$ at a P_{CO_2} of 60 mm Hg was also determined.

Phase 2

Shortly before completion of Phase 1 studies, 12 additional healthy white men of similar age (39.6 ± 8.3 yr; range 24 to 58 yr) were recruited from the same cohort of habitual marijuana-smoking participants who fulfilled the same entry criteria as the subjects in Phase 1. Each also signed an institutionally approved informed consent form and underwent the same preliminary questionnaire and battery of pulmonary function tests. Ventilatory and metabolic measurements were performed at the same time of day on 3 days separated by 1 wk. Subjects were asked to refrain from the same drugs and food products for the same time periods before testing as Phase 1 participants.

On each study day, an intravenous catheter was inserted for serial sampling of blood before and after marijuana smoking for measurement of serum THC by RIA (8). After a 30-min rest, baseline measurements were performed including systolic and diastolic blood pressure, heart rate, subjective assessment of high on a 0 to 100 scale, plethysmographic Raw and FRC (9, 10), and $\dot{V}_E$, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$. The ventilatory and gas-exchange measurements were performed with the patients seated for 5 min using a metabolic cart with rapidly responding infrared CO_2 analyzer and fuel cell O_2 analyzer (Model 2900; Sensormedics, Anaheim, CA); average values recorded during the last 4 min of the measurement period were used in the analysis. Resting metabolic rate was calculated from $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ using the abbreviated equation of Weir (15). After the baseline measurements, subjects smoked a NIDA-supplied marijuana cigarette weighing either 832, 840, or 751 mg assayed at 0% (0 mg), 1.77% (15 mg), or 3.58% (27 mg) THC, respectively, according to a double-blind, randomized crossover design. Marijuana cigarettes were smoked as described previously. Immediately (0 min) and 45, 90, and 135 min after smoking, baseline measurements were repeated. Blood was collected at 1 min, high was assessed at 2 min, heart rate, blood pressure, and temperature were measured at 5 min, body plethysmography at 10 min, and $\dot{V}_E$, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ at 15 min after the start of each measurement period.

Data Analysis

Duplicate measurements of each baseline, presmoking variable were averaged for each subject (Phase 1). Means and standard deviations (SD) of each variable were averaged across all subjects at baseline and at each postsmoking time interval. For each variable, comparisons were made across the three marijuana concentrations (Phase 1, 0, 1.55, and 2.65%; Phase 2, 0, 1.77, and 3.58%) at baseline using a one-way analysis of variance (ANOVA). For each variable and each THC concentration, measurements performed at baseline and at each postsmoking interval were compared using Student's *t* test for paired data. Differences between baseline values and values obtained at each postsmoking measurement interval were also compared across marijuana concentrations using a one-way ANOVA blocking on subjects. When the F test was significant, Tukey's multiple-comparison test was used (16). p Values < 0.05 were considered statistically significant.

Results

The baseline characteristics of the participants in both phases of the study are shown in table 1. Spirometry, lung volumes, and diffusing capacity were essentially within normal limits in all but one subject in Phase 1 who had a moderate obstructive ventilatory defect (FEV_1 55% of predicted; FEV_1/FVC 0.51).

TABLE 1

ANTHROPOMORPHIC DATA, SMOKING HISTORY, AND BASELINE LUNG FUNCTION

	Phase 1 (*n* = 11)		Phase 2 (*n* = 12)	
	Mean	SD	Mean	SD
Age, yr	34.2	7.6	39.6	8.3
Height, cm	178	5.1	175	8.9
Weight, kg	70.2	24.4		
Tobacco smoking				
Cigarettes/day	4.0	9.9	3.3	7.3
Pack-years	2.4	4.8	3.9	8.5
Marijuana smoking				
Joints/day	2.0	1.6	1.9	2.6
Joint-years*	52.2	41.5	56.6	47.9
FVC, % of predicted†	107.2	9.7	109.8	10.8
FEV_1, % of predicted†	105.1	19.9	110.9	16.5
FEV_1/FVC, %	75.5	10.1	78.4	8.1
D_{LCO}, % of predicted‡	89.9	11.5	90.1	14.3

* Number of joints smoked per day times number of years smoked.
† Based on Morris and colleagues (6).
‡ Based on Cotes (7).

Serum THC concentrations for both study phases are shown in table 2. In both phases, the active marijuana preparations caused marked and significant pre- to postcigarette boosts in serum THC levels. Serum THC concentrations peaked shortly after smoking and within 15 min began to decline progressively, although levels remained significantly elevated above the presmoking baseline for at least 45 min (Phase 1) and 135 min (Phase 2) after smoking. Although mean THC levels were higher after the more potent of the two active cigarettes, no statistically significant differences in THC boost were noted between the weaker and the stronger of the active preparations in either phase of the study, with the exception of the 45-min postsmoking interval in Phase 2 (table 2). A small but statistically significant increase in the serum THC level above baseline was observed 2 and 30 min after smoking the placebo preparation in Phase 1, but not Phase 2, of the study, probably a result of residual THC in the placebo preparation that was not completely removed by elution with methanol.

The effects of smoking the different strengths of marijuana on heart rate, high, Raw, and FRC for both phases of the study are shown in table 3. Heart rate

TABLE 2

MEAN (± STANDARD ERROR OF THE MEAN, SEM) SERUM CONCENTRATIONS (ng/ml) OF Δ^9-TETRAHYDROCANNABINOL BEFORE AND AFTER SMOKING MARIJUANA (M)

	Phase 1 (n = 11)			Phase 2 (n = 12)		
	0% M (0 mg THC)	1.55% M (13 mg THC)	2.65% M (20 mg THC)	0% M (0 mg THC)	1.77% M (15 mg THC)	3.58% M (27 mg THC)
Presmoking baseline	11.2 (2.5)	10.7 (3.1)	8.9 (1.5)	5.7 (1.6)	8.7 (3.3)	6.5 (2.7)
Postsmoking, min						
2	18.5 (4.2)	212* (38.6)	293* (76.2)	9.0 (3.6)	170* (35.8)	304* (62.1)
15	18.2 (4.2)	56.2* (9.7)	72.3* (14.2)	–	–	–
30	17.4 (3.8)	43.2* (6.0)	44.8* (6.5)	–	–	–
45	15.0 (3.3)	32.6* (5.2)	35.1* (5.8)	5.1 (1.7)	23.2* (2.9)	39.6*† (7.2)
90	–	–	–	4.9 (1.8)	17.1* (3.1)	22.5* (3.3)
135	–	–	–	4.6 (1.8)	13.9* (2.6)	17.2* (2.4)

* Significantly different from 0% M ($p < 0.05$).
† Significantly different from 1.77% M ($p < 0.05$).

did not change after placebo but increased significantly ($p < 0.01$) and to a similar extent (approximately 36%) within 2 to 5 min after smoking all active marijuana preparations and remained significantly elevated for at least 45 min after smoking 1.55, 1.77, and 2.65% marijuana. All active marijuana cigarettes also produced a comparably significant level of intoxication compared with placebo ($p < 0.05$), which persisted for at least 45 min. FRC did not change after smoking any preparation ($p > 0.9$). In contrast, airway resistance decreased significantly ($p < 0.05$) immediately after smoking all strengths of marijuana, except placebo (0% THC) marijuana, and remained depressed for at least 45 min. No significant differences in the effects of the lower (1.55 or 1.77%) versus the higher potency (2.65 or 3.58%) marijuana preparations on heart rate, high, or airway resistance were noted.

The effects of 0 (placebo), 1.55, and 2.65% (Phase 1) marijuana on ventilatory and $P_{0.1}$ responses to hypercapnia and isocapnic hypoxia are shown in table 4. No significant differences in baseline values for any of the response parameters were found across the 3 days of study. For none of the three marijuana preparations were significant differences noted between pre- and postsmoking values for the slope of the ventilatory or $P_{0.1}$ response to hypercapnia, the P_{CO_2} intercept extrapolated from either of these curves, or $\dot{V}_E$ at a P_{CO_2} of 60 mm Hg. Moreover, no differences in any of the responses to hypercapnia were noted between the different marijuana preparations. In addition, no differences were noted either between pre- and postsmoking hypoxic responses for any potency of marijuana or between the different marijuana strengths.

The effects of 0, 1.77, and 3.58% marijuana (Phase 2) on resting $\dot{V}_E$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and metabolic rate are shown in table 5. No significant differences in baseline values for any of these parameters were noted across the 3 days of study. No significant effect of either strength of active marijuana on resting $\dot{V}_E$, $\dot{V}_{O_2}$, or $\dot{V}_{CO_2}$ or metabolic rate was noted at any time after smoking.

Discussion

The habitual marijuana smokers participating in this study exhibited a significant increase in heart rate, subjective intoxication (high), and decrease in airway resistance after smoking the active preparations of marijuana, but not placebo marijuana. These findings are consistent with the known cardioaccelerator, psychotropic, and bronchodilator effects of THC (2, 17). No dose dependence of these psychophysiologic effects could be demonstrated in either phase of the study. The failure to observe dose-dependent effects might be due, in part, to a smaller puff volume and shorter breath-holding time during the smoking of the more potent preparation, as we noted previously (18), thereby reducing the relative proportion of THC delivered to and retained in the lungs from the more potent (2.65 and 3.54%) cigarettes compared with the less potent (1.35 and 1.67%) preparations. This possibility is supported by the generally comparable pre- to postsmoking boosts in serum THC concentration following the two active cannabis preparations in each phase of the study.

We were unable to demonstrate any significant effects of smoked marijuana containing either 13 or 20 mg THC on ventilatory or $P_{0.1}$ responses to either hypercapnia or hypoxia in our habitual marijuana-smoking subjects. These doses of THC are comparable with those delivered from the recreational smoking of "street" marijuana (500 mg mariju-

TABLE 3

EFFECTS OF SMOKED MARIJUANA ON MEAN (± SEM) HEART RATE, LEVEL OF INTOXICATION (HIGH), AIRWAY RESISTANCE (Raw), AND FRC BEFORE AND 2 AND 45 MIN AFTER SMOKING

	Phase 1 (n = 11)				Phase 2 (n = 12)			
	Heart Rate (min^{-1})	High (0–100)	Raw ($cm\ H_2O/L/s$)	FRC (L)	Heart Rate (min^{-1})	High (0–100)	Raw ($cm\ H_2O/L/s$)	FRC (L)
Placebo (0% M)								
Baseline	72 (3.3)	0 (0)	1.86 (0.31)	3.61 (0.21)	76 (4.5)	0 (0)	2.16 (0.46)	4.20 (0.47)
2 min	73 (3.3)	9 (2.4)	1.78 (0.27)	3.63 (0.24)	76 (4.2)	18 (6.3)	2.09 (0.42)	4.20 (0.43)
45 min	71 (3.3)	4 (2.7)	1.66 (0.29)	3.82 (0.24)	70 (3.6)	11 (3.9)	1.76 (0.36)	4.06 (0.38)
1.55 or 1.77% M								
Baseline	72 (3.9)	0 (0)	2.08 (0.36)	3.73 (0.22)	71 (4.5)	0 (0)	2.67 (0.26)	4.02 (0.33)
2 min	98* (4.5)	38* (6.6)	1.49* (0.26)	3.71 (0.21)	92* (4.8)	45* (8.4)	2.10* (0.20)	4.17 (0.40)
45 min	100* (5.1)	40* (5.1)	1.36* (0.23)	3.89 (0.28)	75 (4.5)	35* (7.8)	1.90* (0.22)	3.98 (0.35)
2.65 or 3.58% M								
Baseline	67 (3.3)	0 (0)	1.97 (0.35)	3.72 (0.19)	74 (3.9)	0 (0)	2.04 (0.24)	4.09 (0.40)
2 min	91* (5.1)	39* (6.3)	1.18* (0.14)	3.73 (0.22)	93* (5.4)	51* (9.6)	1.22* (0.25)	4.10 (0.44)
45 min	89* (3.9)	43* (5.1)	1.18* (0.16)	3.79 (0.22)	81 (5.1)	51* (9.9)	0.99* (0.20)	3.93 (0.36)

* Significantly greater change from baseline compared with placebo ($p < 0.05$); one-way ANOVA followed by Tukey's multiple-comparison test.

TABLE 4

EFFECTS OF SMOKED MARIJUANA (0, 1.55, and 2.65%) ON HYPERCAPNIA AND HYPOXIC VENTILATORY DRIVE (N = 11)

			P_{CO_2} Intercept					
	$\Delta\dot{V}_E/\Delta P_{CO_2}$ (*L/mm Hg*)	$P_{0.1}/\Delta P_{CO_2}$ (*cm H_2O/mm Hg*)	$\dot{V}_E$ Response (*mm Hg*)	$P_{0.1}$ Response (*mm Hg*)	$\dot{V}_E$ at P_{CO_2} mm Hg (*L/min*)	$P_{0.1}$ at P_{CO_2} mm Hg (*cm/H_2O*)	$\Delta\dot{V}_E/\Delta S_{O_2}$ (*L/%*)	$P_{0.1}/\Delta S_{O_2}$ (*cm H_2O/%*)
Placebo (0% M)								
Baseline 1	2.27	0.44	41.8	44.4	40.2	6.57	−1.59	−0.32
	(0.22)	(0.05)	(1.1)	(0.9)	(3.4)	(0.68)	(0.40)	(0.08)
Baseline 2	2.99	0.59	45.4	47.5	42.7	6.80	−1.53	−0.31
	(0.23)	(0.07)	(0.8)	(1.3)	(3.1)	(0.74)	(0.39)	(0.10)
5–15 min	2.94	0.49	43.5	45.2	45.6	7.00	−1.52	−0.29
	(0.31)	(0.05)	(1.5)	(1.2)	(3.8)	(0.73)	(0.42)	(0.10)
35–45 min	3.03	0.55	44.3	45.2	45.8	7.63	−2.01	−0.30
	(0.32)	(0.08)	(1.1)	(3.1)	(4.4)	(0.90)	(0.48)	(0.24)
1.55% M								
Baseline 1	3.41	0.65	44.0	46.1	52.4	8.77	−1.55	−0.30
	(0.46)	(0.09)	(1.3)	(1.3)	(7.5)	(1.45)	(0.35)	(0.08)
Baseline 2	4.16	0.78	45.6	47.5	54.2	8.94	−1.92	−0.33
	(0.71)	(0.12)	(1.0)	(1.4)	(6.9)	(1.63)	(0.45)	(0.08)
5–15 min	3.50	0.59	46.0	46.2	45.9	7.75	−2.55	−0.54
	(0.48)	(0.10)	(1.4)	(1.4)	(5.8)	(1.19)	(0.75)	(0.16)
35–45 min	4.10	0.69	45.5	45.2	48.4	7.80	−1.99	−0.37
	(0.81)	(0.19)	(2.4)	(1.4)	(7.9)	(1.87)	(0.42)	(0.13)
2.65% M								
Baseline 1	3.09	0.55	44.7	46.3	46.8	7.58	−1.62	−0.30
	(0.30)	(0.05)	(0.7)	(1.0)	(5.0)	(0.96)	(0.29)	(0.06)
Baseline 2	3.54	0.66	45.8	46.6	48.3	8.13	−1.48	−0.24
	(0.42)	(0.09)	(1.0)	(1.3)	(5.0)	(0.98)	(0.29)	(0.05)
5–15 min	3.64	0.63	45.9	47.4	47.5	7.42	−1.61	−0.28
	(0.57)	(0.09)	(1.1)	(1.2)	(5.4)	(0.93)	(0.49)	(0.12)
35–45 min	2.91	0.51	43.7	47.3	47.6	6.53	−2.05	−0.41
	(0.27)	(0.05)	(1.5)	(1.7)	(6.3)	(1.15)	(0.55)	(0.17)

* Values represent means; values in parentheses represent ± SEM.

ana containing 1 to 6% THC) or the oral ingestion of U.S. Food and Drug Administration-approved synthetic marijuana (7.5 to 22.5 mg) for control of nausea and vomiting due to cancer chemotherapeutic agents. Our results therefore suggest that THC in doses commonly used either recreationally or medicinally neither stimulates nor depresses central or peripheral chemoreceptor-mediated ventilatory drive in habitual users of marijuana.

These findings are in agreement with those of a previous study (2), which failed to find any effect of a low dose of smoked THC (2.1 and 5.5 mg) on either the slope or the threshold of the hypercapnic ventilatory response curve of healthy, young, experienced marijuana smokers. On the other hand, the present results are at variance with those of two other studies, one demonstrating a depressant (3) and the other a stimulatory (4) effect on hypercapnic drive. In nine young experienced marijuana smokers, Bellville and colleagues (3) found that smoked marijuana containing 19.8 mg THC and oral THC in a dose of 22.5 mg (but not 7.5 mg) both produced a slight, but significant rightward shift of the ventilatory-P_{CO_2} response curve, as indicated by a mean increase of 0.81 to 1.08 mm Hg (smoked marijuana) and 2.50 mm Hg (22.5 mg oral THC) in the P_{CO_2} intercept at a $\dot{V}_E$ of 20 L/min. From these findings, the authors concluded that THC depressed ventilation. However, a subsequent study from the same group (19) failed to find a significant effect of smoked marijuana containing 19.8 mg THC on the hypercapnic ventilatory response slope in habitual users of marijuana. In contrast to these findings, in eight experienced marijuana users, Zwillich and coworkers (4) found that smoked marijuana (500 mg containing 2.2%, or 11 mg, THC) caused a significant increase in the slope of the hypercapnic ventilatory response curve (5.4 ± 1.02 L/min/mm Hg) over the baseline control value (2.7 ± 0.28 L/min/mm Hg), but placebo marijuana had no noticeable effect. In addition, these authors found significant increases in both resting $\dot{V}_E$ and $\dot{V}_{O_2}$ (41 and 28%, respectively) 15 min after active, but not placebo, marijuana. They concluded that smoked marijuana stimulated metabolic rate, ventilation, and the ventilatory response to CO_2. Our inability to demonstrate even a trend toward a stimulatory effect of either low or high doses of THC on hypercapnic ventilatory drive or on resting $\dot{V}_E$ or metabolic rate is in striking contrast to the results of the latter study (4).

The reasons for the discrepancy between the findings of Bellville and associates (3) and Zwillich's group (4), both with one another and with the results of our own study, are not clear but could be due to differences in subject characteristics, the actual dose of THC delivered to the systemic circulation, or methods of measuring and analyzing respiratory drive. First, all three studies, including the present study, employed young male subjects who were all experienced marijuana users, but the sample sizes were small and the intensity and duration of prior exposure of the subjects to marijuana, as well as to other drugs with possible effects on control of breathing, may have differed across the studies. Second, the doses of THC employed in all three studies differed. Vachon and colleagues (2) administered marijuana cigarettes containing relatively low doses of THC (2.3 and 5.5 mg), Bellville and colleagues (3) administered a 900-mg cigarette containing a much higher dose of THC (19.8 mg) and an oral preparation containing 22.5 mg THC, and Zwillich and coworkers (4) employed an inter-

TABLE 5

EFFECTS OF SMOKED MARIJUANA (0, 1.77, AND 3.58% THC) ON RESTING MINUTE VENTILATION ($\dot{V}E$), O_2 CONSUMPTION ($\dot{V}O_2$), CO_2 PRODUCTION ($\dot{V}CO_2$), AND METABOLIC RATE (N = 12)*

	$\dot{V}E$	$\dot{V}O_2$		$\dot{V}CO_2$		Metabolic Rate	
	(L/min)	ml/min	ml/min/kg	ml/min	ml/min/kg	kcal/24 h	kcal/24 h/m²
Placebo (0% M)							
Baseline	11.3	304	3.82	268	3.20	2,090	1,043
	(0.9)	(20.6)	(0.24)	(22.6)	(0.19)	(156)	(56.5)
2 min	10.6	288	3.61	253	3.09	1,997	1,000
	(0.8)	(17.9)	(0.21)	(23.1)	(0.20)	(150)	(56.4)
45 min	10.5	295	3.67	251	3.00	2,033	1,013
	(0.8)	(22.2)	(0.22)	(23.5)	(0.24)	(169)	(64.6)
90 min	10.7	295	3.63	243	2.89	1,976	989
	(0.7)	(23.4)	(0.30)	(20.5)	(0.16)	(159)	(59.5)
135 min	11.0	285	3.54	243	2.94	1,950	981
	(0.8)	(19.6)	(0.23)	(16.2)	(0.12)	(135)	(49.2)
1.77% M							
Baseline	11.1	299	3.67	284	3.37	2,129	1,079
	(1.1)	(17.7)	(0.21)	(25.1)	(0.20)	(145)	(55.0)
2 min	10.2	288	3.50	244	2.96	1,994	1,016
	(0.7)	(16.1)	(0.21)	(18.4)	(0.15)	(126)	(43.1)
45 min	11.2	291	3.46	251	2.96	2,015	1,016
	(0.8)	(20.4)	(0.17)	(21.3)	(0.14)	(152)	(49.4)
90 min	10.9	301	3.57	257	3.05	2,077	1,048
	(0.7)	(19.5)	(0.15)	(21.3)	(0.15)	(146)	(45.4)
135 min	10.4	285	3.50	242	3.09	2,006	1,034
	(0.6)	(25.4)	(0.22)	(19.2)	(0.16)	(183)	(68.5)
3.58% M							
Baseline	10.6	296	3.63	263	3.30	2,077	1,060
	(0.8)	(19.3)	(0.30)	(18.4)	(0.24)	(142)	(55.6)
2 min	10.0	294	3.64	258	3.29	2,081	1,063
	(0.9)	(16.8)	(0.22)	(15.7)	(0.26)	(119)	(51.9)
45 min	10.5	297	3.66	248	3.13	2,069	1,055
	(0.6)	(16.8)	(0.20)	(15.6)	(0.19)	(123)	(50.7)
90 min	11.1	300	3.71	256	3.15	2,092	1,063
	(0.7)	(17.0)	(0.20)	(16.8)	(0.20)	(120)	(44.9)
135 min	11.2	291	3.57	235	3.10	2,032	1,030
	(0.7)	(18.8)	(0.21)	(16.4)	(0.17)	(130)	(49.8)

* Values represent means; values in parentheses represent ± SEM.

mediate dose of THC (11 mg) contained within a 500-mg cigarette. Unlike the latter two authors, we assessed the effects of two different smoked doses of THC (13 and 20 mg) on hypercapnic ventilatory drive, but one or the other of these two doses closely approximated the single smoked dose used by the two previous authors. The smoking technique imposed by these investigators (3, 4) on their subjects was standardized in an effort to minimize variability in the dose of THC delivered to and absorbed from the lower respiratory tract. Unlike the present study, however, these authors did not measure serum levels of THC before and after THC administration to quantitate the actual absorbed dose. Therefore, comparisons between the results of these studies and our own findings could be confounded by differences in the actual boost in blood concentration of THC achieved by smoking or ingestion of THC. Last, previous investigators did not examine other measures of central respiratory drive, such as the mouth occlusion pressure response to hypercapnia, measurement of which, unlike that of ventilatory responses, is unaffected by changes in respiratory system mechanics (20, 21). Since marijuana causes bronchodilation, as demonstrated in the present study as well as previously (2, 17), the associated reduction in the resistive load to breathing could conceivably modify the ventilatory expression of a possible depressant effect of THC on respiratory drive. On the other hand, since THC did not produce any changes in FRC, the $P_{0.1}$ responses we observed would not be expected to be influenced by THC-induced changes in the position or length of the diaphragm (22).

The only previous study evaluating the effect of THC on the ventilatory response to hypoxia was that of Zwillich and colleagues (4) in which a single strength of smoked marijuana containing 11 mg THC did not produce any demonstrable change in the hypoxic ventilatory response. The effect of a higher dose of THC was not studied. In the present study, we were also unable to demonstrate any influence of smoked marijuana containing either 13 or 20 mg THC on the ventilatory or $P_{0.1}$ responses to isocapnic hypoxia. Therefore, these two studies consistently point to an absence of any effect of THC in customary doses on peripheral chemoreceptor-mediated respiratory drive.

Our failure to demonstrate an acute effect of marijuana of mild to moderate potency on control of breathing must be viewed with caution since a "real" effect on respiratory drive might have been masked by the variability of the test or by the development of tolerance. Tolerance has been demonstrated to many of the psychophysiologic effects of marijuana after long-term use, including its effects on heart rate, airway resistance, and high (23), as well as on respiration (19). After demonstrating a small but statistically significant acute depressant effect of marijuana (900 mg, 2.2% THC) on the hypercapnic ventilatory response (1 to 2 mm rightward displacement of the P_{CO_2} threshold) in experienced marijuana users who had refrained from smoking any marijuana for 2 wk, Bellville and colleagues (19) observed that this effect was eliminated 8 to 9 wk after initiation of daily *ad libitum* marijuana intoxication. The subjects we studied were all heavy, habitual users of marijuana and therefore more likely than inexperienced subjects to have developed tachyphylaxis. If tolerance had developed to an effect of THC on control of breathing, resting $\dot{V}E$, or metabolic rate in our subjects, then a larger dose of THC than we evaluated might have been required to counteract the influence of tachyphylaxis. Moreover, since we did not study subjects without prior exposure to marijuana, we cannot be certain that the effect of THC on the regulation of ventilation in such individuals would be similar to that in experienced users. Finally, our data do not exclude the possibility that very high doses of inhaled THC causing severe central nervous system intoxication might have clinically significant effects on ventilatory drive and/or metabolic rate.

Acknowledgment

The writers thank Enoch Lee for his technical assistance, Hunghu Liu for his aid in statistical analysis, and Nancy Marshello and Virginia Reed Hansen for their help in preparing the manuscript.

References

1. Johnston LD, O'Malley PM, Bachman JG. Drug use among American high school seniors, college students and young adults, 1975–1990. Vol. 1. High school seniors. National Institute on Drug Abuse, Rockville, MD: DHHS Publ. (ADM) 91-1813, 1991.
2. Vachon L, Muiris X, Fitzgerald MD, Solliday NH, Gould IA, Gaensler EA. Single-dose effects of marihuana smoke. N Engl J Med 1973; 288: 985–9.
3. Bellville JW, Swanson GD, Aqleh KA. Respiratory effect of delta-9-tetrahydrocannabinol. Clin Pharmacol Ther 1975; 17:541–8.
4. Zwillich CW, Doekel R, Hammill S, Weil JV. The effects of smoked marijuana on methacholine and respiratory control. Am Rev Respir Dis 1978; 118:885–91.
5. Tashkin DP, Coulson AH, Clark VA, *et al.* Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone and nonsmokers. Am Rev Respir Dis 1987; 135: 209–16.
6. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. Am Rev Respir Dis 1971; 103:57–67.
7. Cotes JE. Lung function. Assessment and application in medicine. 4th ed. Oxford: Blackwell Scientific, 1975; 370.
8. Soares JR, Gross SJ. Separate radioimmune measurements of body fluid Δ^9-THC and 11-nor-9-carboxy-1 Δ^9-THC. Life Sci 1976; 19:1711–8.
9. Dubois AB, Botelho SY, Comroe JH Jr. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory diseases. J Clin Invest 1956; 35:327–35.
10. Dubois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH Jr. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J Clin Invest 1956; 35:322–6.
11. Wu T-C, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 1988; 318:347–51.
12. Tashkin DP, Gliederer F, Rose J, *et al.* Tar, CO and Δ^9-THC delivery from the 1st and 2nd halves of a marijuana cigarette. Pharmacol Biochem Behav 1991; 40:651–6.
13. Rebuck AS, Campbell EJM. A clinical method for assessing the ventilatory response to hypoxia. Am Rev Respir Dis 1974; 109:345–50.
14. Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. Aust Ann Med 1967; 16:20–32.
15. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol (Lond) 1989; 109:1–9.
16. Neter J, Wasserman W, Kutner MH. Applied linear statistical models, 2nd ed. Homewood, IL: Richard D. Irwin, Inc., 1985; 547–79.
17. Tashkin DP, Shapiro BJ, Frank IM. Acute pulmonary physiologic effects of smoked marijuana and oral Δ^9-tetrahydrocannabinol in healthy young men. N Engl J Med 1973; 289:336–41.
18. Tashkin DP, Wu T-C, Djahed B, Rose J. Smoking topography and delivery of insoluble particulates and carbon monoxide in the lung during the smoking of tobacco and marijuana of varying potency in habitual smokers of both substances and marijuana alone. In: Cheser G, Consroe P, Musty R, eds. Marijuana: an international report. Proceedings of Melbourne symposium on cannabis September 2–4. National Campaign Against Drug Abuse. Monograph series no. 7. Canberra: Australian Government Publishing Service, 1988; 31–6.
19. Bellville JW, Gasser JC, Miyake T, Aqleh K. Tolerance to the respiratory effects of marijuana in men. J Pharmacol Exp Ther 1976; 197:326–31.
20. Whitelaw WA, Derenne JP, Milic-Emili J. Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 1975; 23:181–99.
21. Milic-Emili J, Whitelaw WA, Grassino AE. Measurement and testing of respiratory drive. In: Hornbein TF, ed. Regulation of breathing. New York: Marcel Dekker, 1981; 675–743.
22. Matthews AW, Howell JBL. The rate of isometric pressure development as a measure of responsiveness to carbon dioxide in man. Clin Sci Mol Med 1975; 49:57–68.
23. Tashkin DP, Shapiro BJ, Lee EY, Harper CE. Subacute effects of heavy marihuana smoking on pulmonary function in healthy men. New Engl J Med 1976; 294:125–9.